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BM Research A/S  
Controlled Release Composition  
Our ref: 4150 PC 1

Dear Sirs,

We hereby submit our reply to the Written Opinion dated 23 November 1995, including new, additional claims 28-33. The further examination should thus be based on claims 1-27 as filed together with the new claims.

As explained in the application, the present invention is a further development based on the inventions disclosed in WO 89/09066 and WO 91/04015 (referred to in the Written Opinion as documents D1 and D2, respectively), which relate to controlled release compositions containing a matrix of a crystalline polyethylene glycol polymer with a non-ionic emulsifier dispersed therein, and an active substance dispersed either throughout the matrix or in certain zones within the matrix. The advantage of these compositions is that water diffusion in the interface between the polymer crystals is substantially eliminated, whereby erosion of the matrix containing the active substance is predominantly effected by the dissolving action of an aqueous medium on any surfaces of the composition exposed to the aqueous medium into which the active substance is to be released.

The controlled release compositions of D1 and D2 were found to provide excellent results in terms of obtaining the desired controlled release pattern for the composition in question, but the problem remained as to how to provide these compositions with a slowly erodible coating that can function in a manner complementary to the controlled erosion of the matrix containing the active substance, so that erosion of the matrix and concomitant release of the active substance occurs only at one or more given surfaces of the matrix exposed to the aqueous medium. In particular, it was desirable to on the one hand provide a



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coating that, while still uneroded, is substantially impenetrable to the aqueous medium in which the composition is designed to be used, and on the other hand slowly crumbles or erodes upon exposure to the aqueous medium, but at a rate that is equal to or slower than the erosion rate of the matrix containing the active substance.

The present inventors found that the claimed coating containing the first cellulose derivative and at least one of a second cellulose derivative, a plasticizer and a filler was able to provide these desired characteristics for the coating, and that such a coating functions in the intended manner together with the slowly erodible matrix containing the active substance. As a result, erosion of the matrix and release of the active substance takes place only from the surface or surfaces that are not covered by the coating (i.e. not from all of the surfaces of the matrix), but the coating still has the advantage of being slowly eroded, which means that there are no problems of a hard, empty coating remaining e.g. in the body of a person taking such a composition for controlled release of a medicament.

Turning now to the Written Opinion, the Examiner has expressed the view that the claimed invention lacks inventive step in the light of D3 (DE-A-2 415 490), which discloses similar coating compositions based on different types of cellulose derivatives. We believe it is important in this regard to look at the nature of that which is disclosed in D3. Although it is correct that D3 discloses coating compositions for solid medicines, D3 is not involved with coating a controlled release matrix such as that of the present invention, but rather with the coating of individual granules of a medicament, these granules being subsequently formed into tablets. It is particularly significant that according to D3, the individual medicament granules are completely coated by the coating compositions, in contrast to the present invention, in which a controlled release matrix is selectively coated so that the composition contains at least one opening exposing at least one surface of the matrix. The coatings of D3 are designed to not dissolve in gastric fluid and to dissolve in intestinal fluid at a suitable rate, but there is no problem in D3 in terms of coordinating the erosion of a controlled release matrix with the erosion of the coating; in D3, once the coating on the granules has eroded sufficiently to expose the medicament granules to the intestinal fluid, the medicament is released. In contrast, erosion of the coating of the present invention is linked to erosion of the matrix in order to ensure that the matrix surface area exposed to the aqueous mediums remains substantially constant. The coating of the claimed compositions is thus not a conventional coating in the sense of e.g. D3, which represents a basic difference between the two. An opening in the coating of D3 would obviously defeat the whole purpose of that coating, since the medicament being coated in D3 is in the conventional form of granules and not embedded in a controlled release matrix.

Related to the fact that D3 is dealing with the coating of a medicament in conventional granule form is the fact that the coating methods disclosed in D3 are also conventional, e.g. pan coating and fluidizing coating methods. As

explained in the present application, extrusion and injection moulding methods are particularly suitable for producing the compositions of the invention. Such methods were clearly not contemplated in D3, and are furthermore not even possible for compositions of the type disclosed in D3. This represents an important advantage of the present invention, since production methods such as co-extrusion and injection moulding of the matrix and coating are particularly suitable for mass production of the controlled release compositions. This important aspect of the invention, which is disclosed in the application as filed at pages 15-16 and in the examples, has been made the subject matter of new claims 28-33.

For the reasons given above, we respectfully submit that the subject matter of the claims involves an inventive step.

Finally, we request an additional opportunity to submit amendments and/or arguments, pursuant to Rule 66.4(b) PCT, in the event the Examiner believes that there are any outstanding issues that need to be addressed with regard to the patentability of the claims.

Yours sincerely,

Plougmann, Vingtoft & Partners



Jeff Salka

Claims 28-33  
Form 1037

28. A method for producing a composition for controlled  
5 delivery of at least one active substance into an aqueous  
medium by erosion at a preprogrammed rate of at least one  
surface of the composition, the method comprising forming, by  
means that include extrusion or injection moulding,  
i) a matrix comprising the active substance, the matrix  
10 being erodible in the aqueous medium in which the  
composition is to be used, and  
ii) a coating having at least one opening exposing at  
least one surface of said matrix, the coating  
comprising  
15 a) a first cellulose derivative which has thermoplastic  
properties and which is substantially insoluble in  
the aqueous medium in which the composition is to be  
used,  
and at least one of  
20 b) a second cellulose derivative which is soluble or  
dispersible in water,  
c) a plasticizer, and  
d) a filler,  
said coating being a coating which crumbles and/or erodes  
25 upon exposure to the aqueous medium, in particular a body  
fluid, at a rate which is equal to or slower than the rate at  
which the matrix erodes in the aqueous medium, allowing  
exposure of said surface of the matrix to the aqueous medium  
to be controlled.
- 30 29. A method according to claim 28 wherein the composition is  
produced by co-extrusion of a) the matrix material with the  
active substance dispersed therein and b) the coating.
30. A method according to claim 28 wherein the composition is  
produced by injection moulding of the coating and subsequent

injection moulding of the matrix containing the active substance.

31. A method according to claim 28 wherein the composition is produced by injection moulding of the coating and subsequent  
5 injection moulding of alternating layers comprising at least one layer comprising matrix material and at least one layer comprising the active substance.

32. A method according to claim 28 wherein the composition is produced by injection moulding of the matrix containing the  
10 active substance, or injection moulding of alternating layers comprising at least one layer comprising matrix material and at least one layer comprising the active substance, into a pre-formed tube which forms the coating.

33. A method according to claim 28 wherein the composition is  
15 formed by extrusion or injection moulding of the matrix containing the active substance followed by dip coating.